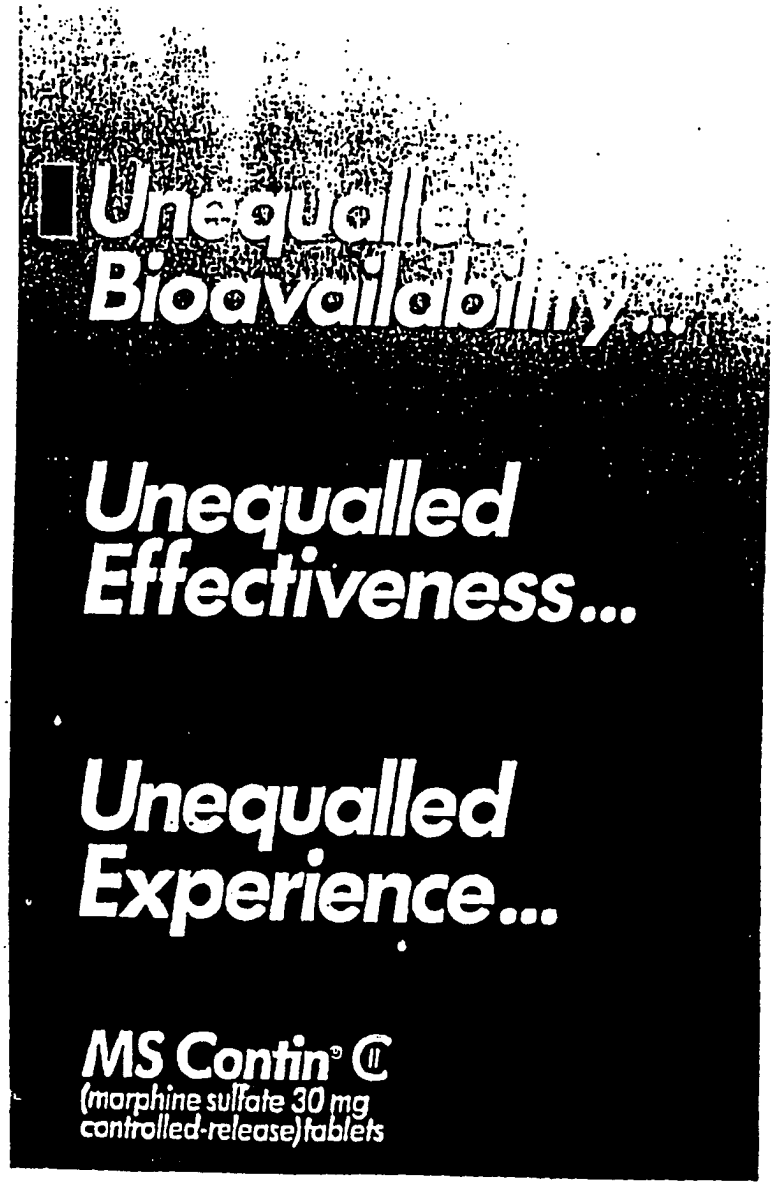
BS

MS Contin is Unequalled...



P 041765

6/19/02 GCB

Unequalled Bioavailability...

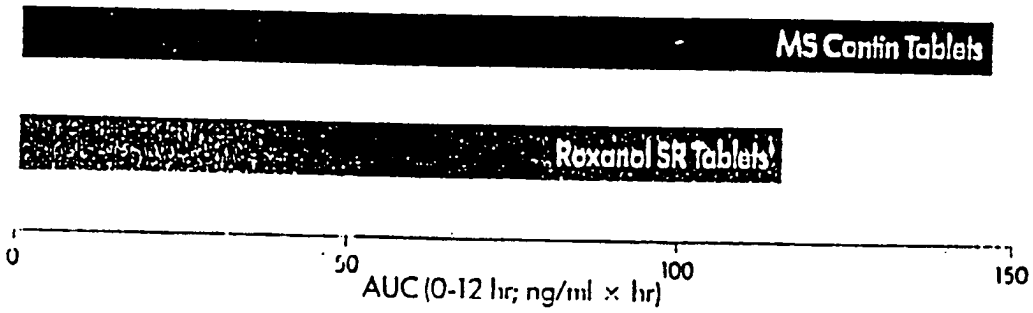
MS Contin has superior 12-hour bioavailability:

MS Contin is 27% more bioavailable than Roxanol SR.

Bioavailability:
"The extent to which a drug reaches its site of action or a biological fluid from which the drug has access to its site of action."

[illegible]

Bioavailability (0-12 hr) of MS Contin 30 mg Tablets vs. Roxanol SR 30 mg Tablets as determined by plasma drug levels in a crossover study in 18 normal volunteers†



Important Note: While there is an indirect relationship between plasma morphine levels and analgesia, higher plasma levels are generally associated with superior relief of pain, as demonstrated in the literature. There is a lag time or hysteresis between the time of peak plasma morphine levels and the time of peak drug effects."

[illegible]

12-Hour MS Contin...

MS Contin® (morphine sulfate 30 mg controlled-release) tablets C II

- *No other morphine product is bioequivalent to MS Contin.*
- *MS Contin and Roxanol SR are not bioequivalent, therefore, Roxanol SR is not therapeutically interchangeable with MS Contin.*[1,11]
- *MS Contin reaches a significantly higher peak concentration, for more effective analgesia.*

Bioequivalence:
"They [pharmaceutical formulations] are said to be biologically equivalent if they yield similar concentrations of drug in blood and tissues...Pharmaceutical preparations that are chemically equivalent but not biologically or therapeutically equivalent are said to differ in their bioavailability."

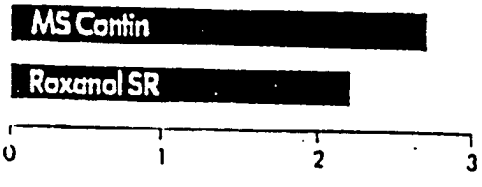
The three criteria for bioequivalency are comparable...

1. bioavailability (calculated from area under the time-concentration-curve)
2. time to peak plasma concentration
3. peak concentration

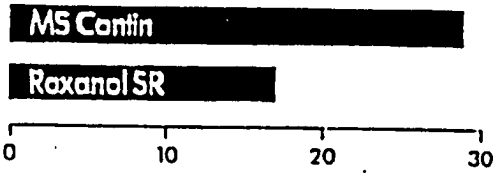
Results of Comparative Study[1]

	MS Contin (2 × 30 mg)	Roxanol SR (2 × 30 mg)
AUC	147 (0-12 hr; ng/ml × hr)	116
T_{max} (hrs)	2.7	2.2
C_{max} (ng/ml)	29	17

Time to Peak Concentration (T_{max})[1]



Peak Concentration (C_{max})[1]



Proven Against Cancer Pain

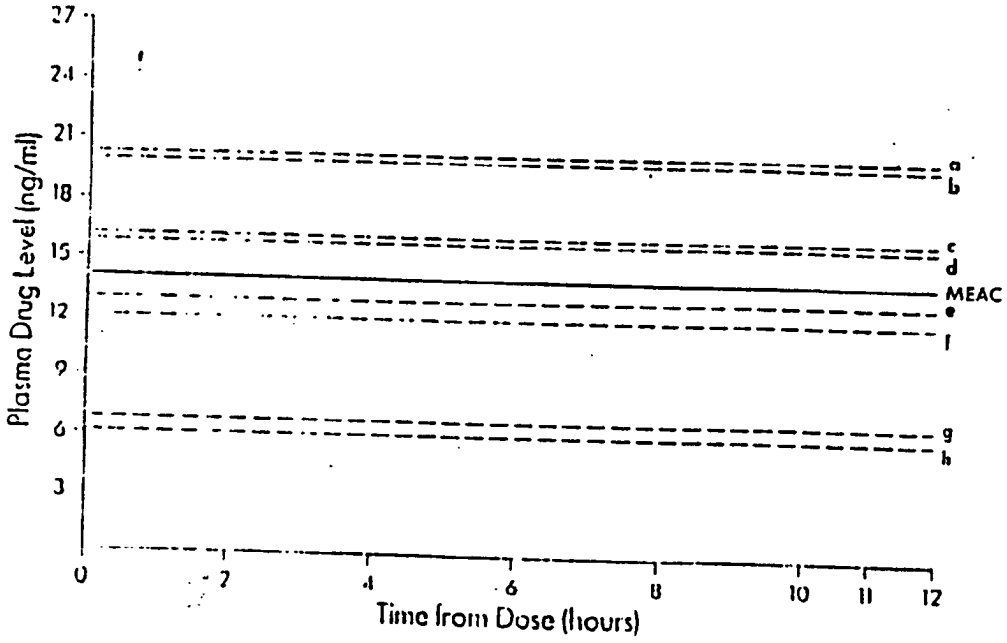
P 041767

Unequalled Effectiveness...

What is the effective analgesic level of oral morphine?

A careful review of the literature[a-h] indicates the complexity of defining effective analgesic plasma morphine levels. However, there is generally a "Minimally Effective Analgesic Concentration" (MEAC) of plasma morphine below which no analgesia is provided (see Chart below).

Minimally Effective Analgesic Concentrations (MEAC) of Morphine



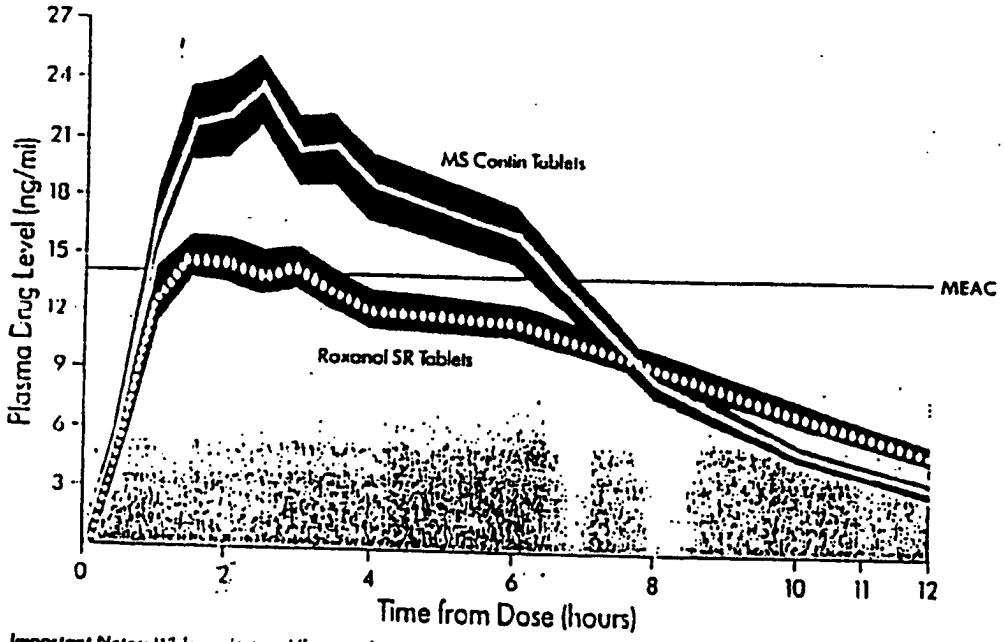
[a-h] ...

12-Hour MS Contin[®]...

MS Contin® (morphine sulfate 30 mg controlled-release) tablets C II

- MS Contin achieves significantly higher analgesic concentrations.[1,11]
- MS Contin maintains plasma levels above the minimally effective analgesic concentration (MEAC) significantly longer.

Plasma morphine concentration (mean ± SE) following equal doses of MS Contin and Roxanol SR†



Important Note: Wide qualitative differences between morphine formulations are unlikely to vary among subject groups, the absolute magnitude of plasma morphine levels and pharmacokinetic parameters observed here in young normal subjects are likely to be different from those in older subjects and in patients with advanced disease. For example, the apparent plasma morphine elimination half-life can be expected to be prolonged in such patients.

Additionally, there is a lag time, or hysteresis, between the time of peak plasma morphine levels and the time of peak drug effects.[11]

Proven Against Cancer Pain

P 041769

Unequalled Experience...

- Extensive published clinical documentation that supports 12-hour efficacy and safety[1-14]
- Over 6 years' proven clinical experience with over a half-million prescriptions[1]
- MS Contin has a clinically documented safety profile:
  In over 95% of patients, side effects were fewer or equal to pre-study analgesic[15-17]

Percent of patients experiencing fewer or equal side effects[15-17]

Study #1: Memorial Sloan-Kettering Cancer Center

55% of patients experienced fewer side effects
21% of patients experienced equal side effects

Study #2: New York University School of Medicine

94% of patients experienced fewer side effects
6% of patients experienced equal side effects

Study #3: Bowman Gray School of Medicine

52% of patients experienced fewer side effects
48% of patients experienced equal side effects

12-Hour MS Contin...

MS Contin® (morphine sulfate 30 mg controlled-release) tablets Ⓒ II

- *MS Contin is the subject of two international symposia on pain control.*[18-19]
- *Safety and efficacy demonstrated at prestigious cancer treatment centers in over 1200 study patients.*
- *Professional educational support:*
  Speakers' Bureau; Educational Slides and Videotapes, including "Cancer Pain Management" Chaired by Dr. Kathleen M. Foley of Memorial Sloan-Kettering Cancer Center.
- *MS Contin Tablets are small, round and film coated.*
  Their distinctive lavender color makes them easy to recognize and identify. Their small size (less than half that of Roxanol SR) makes them easy to swallow.

[illegible]

Proven Against Cancer Pain

MS Contin® is Unequalled...

The only 12-hour oral narcotic analgesic proven against cancer pain.

- Superior 12-hour bioavailability – 27% more bioavailable than Roxanol SR.
- No other morphine product is bioequivalent to MS Contin; therefore, none is therapeutically interchangeable.
- Achieves a significantly higher peak concentration – for more effective analgesia.
- Maintains plasma morphine levels above the minimally effective analgesic concentration (MEAC) significantly longer – for effective pain relief.
- Published clinical documentation of superior or equal efficacy compared to immediate-release morphine and other oral opioid analgesics.
- Proven safety profile – published clinical documentation shows fewer side effects than previous analgesic (Hydromorphone, Methadone, Oxycodone, Codeine, Meperidine).

Also available

MSIR® Useful in starting patients on morphine or for treating breakthrough or incident pain.

(morphine sulfate) 15 mg and 30 mg Immediate-Release tablets C II

12-hour MS Contin® C II

(morphine sulfate 30 mg controlled-release) tablets

Proven Against Cancer Pain

For Prescribing Information Please See Accompanying Professional Literature

Purdue Frederick 8214J PM28

P 041772

[illegible]

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression in the neonate.

Nursing Mothers

Low levels of morphine have been detected in the breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving MS CONTIN since morphine may be excreted in the milk.

Pediatric Use

MS CONTIN has not been evaluated systematically in children.

ADVERSE REACTIONS:

The adverse reactions caused by morphine are essentially those observed with other opioid analgesics. They include the following major hazards: respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

Most Frequently Observed

Constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating, dysphoria and euphoria.

Some of these effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. Some adverse reactions in ambulatory patients may be alleviated if the patient lies down.

Less Frequently Observed Reactions

Central Nervous System: Weakness, headache, agitation, tremor, uncoordinated muscle movements, seizure, alterations of mood (nervousness, apprehension, depression, floating feelings), dreams, muscle rigidity, transient hallucinations and disorientation, visual disturbances, insomnia and increased intracranial pressure.

Gastrointestinal: Dry mouth, constipation, biliary tract spasm, laryngospasm, anorexia, diarrhea, cramps and taste alterations.

Cardiovascular: Flushing of the face, chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension and hypertension.

Genitourinary: Urine retention or hesitancy, reduced libido and/or potency.

Dermatologic: Pruritus, urticaria, other skin rashes, edema and diaphoresis.

Other: Antidiuretic effect, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia and miosis.

DRUG ABUSE AND DEPENDENCE:

Opioid analgesics may cause psychological and physical dependence (see WARNINGS). Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with narcotic antagonist activity, e.g., naloxone [illegible] (see OVERDOSAGE). Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued narcotic usage. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and, subsequently, by decreases in the intensity of analgesia.

[illegible]

OVERDOSAGE:

[illegible]

[illegible] administered. Use of a narcotic antagonist in such a person should be avoided. If necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

DOSAGE AND ADMINISTRATION:

(See also: CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS sections)

MS CONTIN TABLETS ARE TO BE TAKEN WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED.

TAKING BROKEN, CHEWED OR CRUSHED MS CONTIN TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

MS CONTIN is intended for use in patients who require more than several days continuous treatment with a potent opioid analgesic. The controlled-release nature of the formulation allows it to be administered on a more convenient schedule than conventional immediate-release oral morphine products. (See CLINICAL PHARMACOLOGY: "Metabolism and Pharmacokinetics.") However, MS CONTIN does not release morphine continuously over the course of a dosing interval. The administration of single doses of MS CONTIN on a q12h dosing schedule will result in higher peak and lower trough plasma levels than those that occur when an identical daily dose of morphine is administered using conventional oral formulations on a q4h regimen. The clinical significance of greater fluctuations in morphine plasma level has not been systematically evaluated.

As with any potent opioid drug product, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of initial dose and dosing interval of MS CONTIN, attention should be given to 1) the daily dose, potency and precise characteristics of the opioid the patient has been taking previously (e.g., whether it is a pure agonist or mixed agonist/antagonist), 2) the reliability of the relative potency estimate used to calculate the dose of morphine needed (N.B. potency estimates may vary with the route of administration), 3) the degree of opioid tolerance, if any, and 4) the general condition and medical status of the patient.

The following dosing recommendations, therefore, can only be considered suggested approaches to what is actually a series of clinical decisions in the management of the pain of an individual patient.

Conversion from Conventional Oral Morphine to MS CONTIN

A patient's daily morphine requirement is established using immediate-release oral morphine (dosing every 4 to 6 hours). The patient is then converted to MS CONTIN in either of two ways: 1) by administering one-half of the patient's 24-hour requirement as MS CONTIN on an every 12-hour schedule; or, 2) by administering one-third of the patient's daily requirement as MS CONTIN on an every eight hour schedule. With either method, dose and dosing interval is then adjusted as needed (see discussion below). The 15 mg tablet should be used for initial conversion for patients whose total daily requirement is expected to be less than 60 mg. The 30 mg tablet strength is recommended for patients with a daily morphine requirement of 60 to 120 mg. When the total daily dose is expected to be greater than 120 mg, the appropriate combination of tablet strengths should be employed.

Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to MS CONTIN

MS CONTIN can be administered as the initial oral morphine drug product; in this case, however, particular care must be exercised in the conversion process. Because of uncertainty about, and intersubject variation in, relative estimates of opioid potency and cross tolerance, initial dosing regimens should be conservative; that is, an underestimation of the 24-hour oral morphine requirement is preferred to an overestimate. To this end, initial individual doses of MS CONTIN should be estimated conservatively. In patients whose daily morphine requirements are expected to be less than or equal to 120 mg per day, the 30 mg tablet strength is recommended for the initial titration period. Once a stable dose regimen is reached, the patient can be converted to the 60 mg or 100 mg tablet strength, or appropriate combination of tablet strengths, if desired.

Estimates of the relative potency of opioids are only approximate and are influenced by route of administration, individual patient differences, and possibly, by an individual's medical condition. Consequently, it is difficult to recommend any fixed rule for converting a patient to MS CONTIN directly. The following general points should be considered, however:

1. *Parenteral to oral morphine ratio:* Estimates of the oral to parenteral potency of morphine vary. Some authorities suggest that a dose of oral morphine only three times the daily parenteral morphine requirement may be sufficient in chronic use settings.

2. *Other parenteral or oral opioids to oral morphine:* Because there is lack of systematic evidence bearing on these types of analgesic substitutions, specific recommendations are not possible. Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate. In general, it is safer to underestimate the daily dose of MS CONTIN required and rely upon ad hoc supplementation to deal with inadequate analgesia. (See discussion which follows.)

Use of MS CONTIN as the first opioid analgesic

There has been no systematic evaluation of MS CONTIN as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient using a controlled-release morphine, it is ordinarily advisable to begin treatment using an immediate-release formulation.

Considerations in the Adjustment of Dosing Regimens

Whatever the approach, if signs of excessive opioid effects are observed early in a dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, "breakthrough" pain occurs late in the dosing interval, the dosing interval may be shortened. Alternatively, a supplemental dose of a short-acting analgesic may be given. As experience is gained, adjustments can be made to obtain an appropriate balance between pain relief, opioid side effects, and the convenience of the dosing schedule.

In adjusting dosing requirements, it is recommended that the dosing interval never be extended beyond 12 hours because the administration of very large single doses may lead to acute overdose. (N.B. MS CONTIN is a controlled-release formulation; it does not release morphine continuously [illegible]

[illegible] the 15 mg tablet should be used.

Conversion from MS CONTIN to parenteral opioids: When converting a patient from MS CONTIN to parenteral opioids, it is best to assume that the parenteral to oral potency is high. NOTE THAT THIS IS THE CONVERSE OF THE STRATEGY USED WHEN THE DIRECTION OF CONVERSION IS FROM THE PARENTERAL TO ORAL FORMULATIONS. IN BOTH CASES, HOWEVER, THE AIM IS TO ESTIMATE THE NEW DOSE CONSERVATIVELY. For example, to estimate the required 24-hour dose of morphine for IM use, one could employ a conversion of 1 mg of morphine IM for every 6 mg of morphine as MS CONTIN. Of course, the IM 24-hour dose would have to be divided by six and administered on a q4h regimen. This approach is recommended because it is least likely to cause overdose.

HOW SUPPLIED:

NDC 0034-0514-10: MS CONTIN (morphine sulfate controlled-release tablets) 15 mg are supplied in opaque plastic bottles containing 100 tablets.

NDC 0034-0514-50: MS CONTIN (morphine sulfate controlled-release tablets) 15 mg are supplied in opaque plastic bottles containing 500 tablets.

NDC 0034-0514-25: MS CONTIN (morphine sulfate controlled-release tablets) 15 mg are supplied in unit dose packaging with 25 individually numbered tablets per card (numbered in descending order for easier counting) and shrink-wrapped in inner packs of 100 tablets (4 cards of 25 tablets per card). One shipper contains 300 tablets (3 inner packs of 100 tablets each). Each individual tablet-unit is labeled "MS CONTIN CR, 15 mg."

NDC 0034-0515-50: MS CONTIN (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 50 tablets.

NDC 0034-0515-10: MS CONTIN (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 100 tablets.

NDC 0034-0515-45: MS CONTIN (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 250 tablets.

NDC 0034-0515-50: MS CONTIN (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 500 tablets.

NDC 0034-0515-25: MS CONTIN (morphine sulfate controlled-release tablets) 30 mg are supplied in unit dose packaging with 25 individually-numbered tablets per card (numbered in descending order for easier counting) and shrink-wrapped in inner packs of 100 tablets (4 cards of 25 tablets per card). One shipper contains 300 tablets (3 inner packs of 100 tablets each). Each individual tablet-unit is labeled "MS CONTIN CR 30 mg."

NDC 0034-0516-10: MS CONTIN (morphine sulfate controlled-release tablets) 60 mg are supplied in opaque plastic bottles containing 100 tablets.

NDC 0034-0516-50: MS CONTIN (morphine sulfate controlled-release tablets) 60 mg are supplied in opaque plastic bottles containing 500 tablets.

NDC 0034-0516-25: MS CONTIN (morphine sulfate controlled-release tablets) 60 mg are supplied in unit dose packaging with 25 individually numbered tablets per card (numbered in descending order for easier counting) and shrink-wrapped in inner packs of 100 tablets (4 cards of 25 tablets per card). One shipper contains 300 tablets (3 inner packs of 100 tablets each). Each individual tablet-unit is labeled "MS CONTIN CR, 60 mg."

NDC 0034-0517-10: MS CONTIN (morphine sulfate controlled-release tablets) 100 mg are supplied in opaque plastic bottles containing 100 tablets.

NDC 0034-0517-50: MS CONTIN (morphine sulfate controlled-release tablets) 100 mg are supplied in opaque plastic bottles containing 500 tablets.

NDC 0034-0517-25: MS CONTIN (morphine sulfate controlled-release tablets) 100 mg are supplied in unit dose packaging with 25 individually numbered tablets per card (numbered in descending order for easier counting) and shrink-wrapped in inner packs of 100 tablets (4 cards of 25 tablets per card). One shipper contains 300 tablets (3 inner packs of 100 tablets each). Each individual tablet-unit is labeled "MS CONTIN CR 100 mg."

15 mg: Each round, blue colored tablet bears the symbol PF on one side and M15 on the other side.

30 mg: Each round, lavender colored tablet bears the symbol PF on one side and M30 on the other side.

60 mg: Each round, orange colored tablet bears the symbol PF on one side and M60 on the other side.

100 mg: Each round, gray-colored tablet bears the symbol PF on one side and 100 on the other side.

Store tablets at controlled room temperature 15-30°C (59-86°F).

Dispense in tight, light-resistant container.

CAUTION:

DEA Order Form Required.

Federal law prohibits dispensing without prescription.

THE PURDUE FREDERICK COMPANY
NORWALK, CT 06850-3590

U.S. Patent Numbers 3965256 and 4235870

September 3, 1991

[illegible]

P 041773

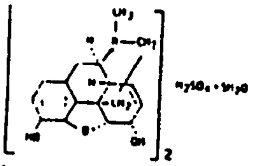
MS CONTIN® 30 mg Tablets
MS CONTIN® 60 mg Tablets
MS CONTIN® 100 mg Tablets
Morphine Sulfate Controlled-Release CII

WARNING: May be habit forming.

E3220

DESCRIPTION:

[illegible] morphine sulfate is 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate and has the following structural formula



Each MS CONTIN 15 mg Controlled Release Tablet contains: 15 mg Morphine Sulfate U.S.P. Inactive ingredients: Cetostearyl Alcohol, FD&C Blue No. 2, Hydroxyethyl Cellulose, Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Talc, Titanium Dioxide and other ingredients.

Each MS CONTIN 30 mg Controlled Release Tablet contains: 30 mg Morphine Sulfate U.S.P. Inactive ingredients: Cetostearyl Alcohol, D&C Red No. 7, FD&C Blue No. 1, Hydroxyethyl Cellulose, Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Talc, Titanium Dioxide and other ingredients.

Each MS CONTIN 60 mg Controlled Release Tablet contains: 60 mg Morphine Sulfate U.S.P. Inactive ingredients: Cetostearyl alcohol, D&C Red No. 30, D&C Yellow No. 10, Hydroxyethyl Cellulose, Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Talc, Titanium Dioxide and other ingredients.

Each MS CONTIN 100 mg Controlled-Release Tablet contains: 100 mg Morphine Sulfate U.S.P. Inactive ingredients: Cetostearyl Alcohol, Hydroxyethyl Cellulose, Hydroxypropyl Methylcellulose, Magnesium Stearate, Synthetic Black Iron Oxide, Talc, Titanium Dioxide and other ingredients.

CLINICAL PHARMACOLOGY:

Metabolism and Pharmacokinetics

MS CONTIN is a controlled release tablet containing morphine sulfate. [illegible]

[illegible]

PHARMACODYNAMICS:

The effects described below are common to all morphine-containing products.

Central Nervous System

[illegible]

Gastrointestinal Tract and Other Smooth Muscle

[illegible]

Cardiovascular System

[illegible]

INDICATIONS AND USAGE:

MS CONTIN is a controlled release oral morphine formulation indicated for the relief of moderate to severe pain. [illegible]

CONTRAINDICATIONS:

MS CONTIN is contraindicated in patients with known hypersensitivity to the drug, [illegible]

WARNINGS: (See also: CLINICAL PHARMACOLOGY)

Impaired Respiration

[illegible]

Head Injury and Increased Intracranial Pressure

[illegible]

Hypotensive Effect

[illegible]

Interactions with other CNS Depressants

[illegible]

Drug Dependence

[illegible]

PRECAUTIONS: (See also: CLINICAL PHARMACOLOGY)

General

[illegible]

Information for Patients

[illegible]

Drug Interactions (See WARNINGS)

[illegible]

Carcinogenicity/Mutagenicity/Impairment of Fertility

[illegible]

Pregnancy

[illegible]

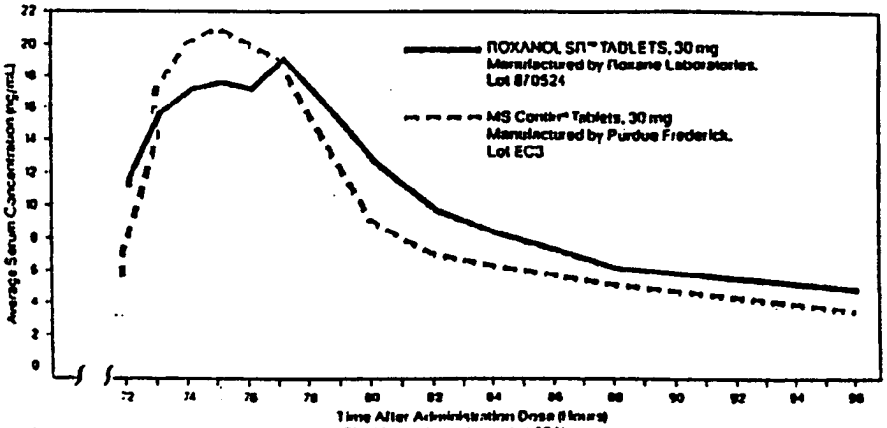
Labor and Delivery

[illegible]

P 041774

AR

AVERAGE SERUM CONCENTRATIONS OF
MORPHINE FOR ROXANOL SR™ TABLETS AND MS CONTIN® TABLETS
Steady State (Multiple Dose) Study (30 mg every 12 hours x 7 doses)



Adapted from Abstracts of the 1988 American Society of Clinical Oncologists Meeting

Multiple-dose randomized crossover trial demonstrates Roxanol SR and MS Contin are bioequivalent.

- Evaluations of standard pharmacokinetic parameters (AUC 72-96 hr, AUC 72-84 hr, Cmax and Cavg) showed less than 10% difference between the two sustained release morphine treatments.
- The investigators concluded that Roxanol SR is bioequivalent to MS Contin.

More cost-effective than MS Contin

- Roxanol SR offers greater cost containment benefits for hospitals.*
- Roxanol SR is a greater value for patients who need relief of chronic cancer pain.*

*[illegible]

ROXANOL SR™ Tablets 30 mg

(Morphine Sulfate Sustained Release Tablets)

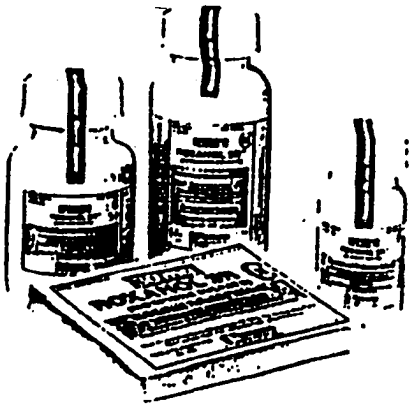
WARNING: May be habit forming.

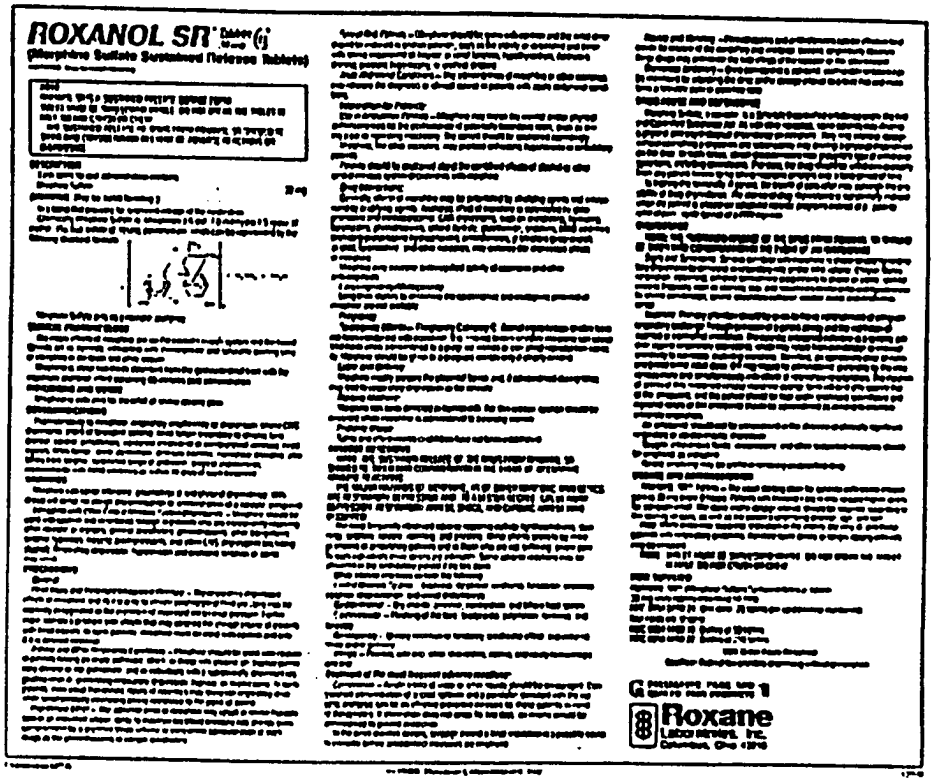
P 041775

Dosing and Administration

The patients should first be stabilized on Roxanol Concentrated Oral Solution. Convert to Roxanol SR by dividing the total daily Roxanol requirement (in milligrams) by three and administering as Roxanol SR Tablets every eight hours. The dose and dosage schedule can be adjusted for greater flexibility according to severity of pain as well as for the patient's underlying disease, age, and size.

Tablets must be swallowed whole...not broken, crushed, or chewed. Tablets have a methyl cellulose coating for easier swallowing.





ROXANOL SR

Roxane